

REMARKS

In an Advisory Action mailed on July 22, 2008, the Examiner entered the amendments made in response to the Final Office Action mailed on April 4, 2008, but maintained the rejection of claims 22-53. By this paper, Applicants have amended claims 22, 32, 40, and 51 and added new claim 54 for clarification of certain features to expedite allowance of the present application. These amendments do not add any new matter. Upon entry of these amendments, claims 22-54 will be pending in the present application and are believed to be in condition for allowance. In view of the foregoing amendments and the following remarks, Applicants respectfully request reconsideration and allowance of all pending claims.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

In the Advisory Action, the Examiner withdrew the rejection of claims 22-39 and 43-48 under 35 U.S.C. § 112, second paragraph, made in the Final Office Action. Specifically, the Examiner stated that the rejection "is withdrawn in view of Applicants' arguments found on page 3, 2nd full paragraph of the remarks." Advisory Action, p. 2. Although the Examiner did not explicitly mention that the rejection of dependent claim 50 under 35 U.S.C. § 112, second paragraph was withdrawn, Applicants assume this to be the case, as claim 50 ultimately depends from claim 32 for which the Examiner has withdrawn the rejection.

Claim Rejections under 35 U.S.C. § 102

In the Advisory Action, the Examiner maintained the rejection of claims 22-29, 32-37, and 40-53 under 35 U.S.C. § 102(b) as being anticipated by Mattes (U.S. Patent 5,759,514, hereinafter "Mattes"). Applicants respectfully traverse this rejection.

Legal Precedent and Guidelines

Anticipation under section 102 can be found only if a single reference shows exactly what is claimed. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 U.S.P.Q. 773 (Fed. Cir. 1985). For a prior art reference to anticipate under section 102, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). To maintain a proper rejection under section 102, a single reference must teach each and every limitation of the rejected claim. *Atlas Powder v. E.I. du Pont*, 750 F.2d 1569 (Fed. Cir. 1984). Accordingly, the Applicants need only point to a single element not found in the cited reference to demonstrate that the cited reference fails to anticipate the claimed subject matter. The prior art reference also must show the identical invention “in as complete detail as contained in the ... claim” to support a *prima facie* case of anticipation. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q. 2d 1913, 1920 (Fed. Cir. 1989).

Deficiencies of Mattes

Turning now to the claims, independent claims 22, 32, 40 and 51, as amended, recite, *inter alia*, “wherein the intercalating moiety is functionalized with a ligand configured to coordinate a [metal(CO)₃]⁺ moiety; and a metal complexed with the ligand attached to the intercalating moiety.” (Emphasis added). This amendment is supported by the specification, which states that the intercalating moieties “are functionalized with ligands able to coordinate the [M(CO)₃]⁺ moiety.” Specification, para. [0010]. Further support and clarification of the phrase “functionalized with ligands,” is provided both in the specification and also in the figures by the procedures used to attach the coordinating function to the intercalating moiety. Specifically, FIGS. 3 and 7 show the functionalization of an intercalating compound to have an attached coordinating compound. *See also, id.*, at paras. [0054]-[0080] (discussing the synthesis procedures shown in FIG. 7 for functionalizing intercalators with a coordinating functionality).

In contrast, Mattes does not disclose any ligands specifically attached to an intercalating moiety, much less ligands attached for the purpose of coordinating to $[M(CO)_3]^+$ moieties. Instead, Mattes discloses attaching a radionuclide directly to an intercalating small molecule by standard oxidative iodination. *See* Mattes, col. 2, ll. 41-43 (“Many nucleic acid binding and DNS-intercalating small molecules suitable in practising this invention can be radiolabeled by standard oxidative iodination.”). Further, all examples provided by Mattes use oxidative iodination to attach a radionuclide directly to the intercalating small molecule. *See, e.g., id.* at col. 4, ll. 66-67; and col. 5, ll. 1-2. Thus, Mattes does not teach or suggest that “the intercalating moiety is functionalized with a ligand configured to coordinate a $[metal(CO)_3]^+$ moiety,” or that a metal is “complexed with the ligand attached to the intercalating moiety” as recited in the present claims. Accordingly, for at least these reasons, Mattes cannot anticipate independent claims 22, 32, 40 and 51.

Furthermore, as amended, independent claim 32 recites “a metal complexed with the ligand attached to the intercalating moiety, wherein the metal comprises Tc-99m, Re-186, Re-188, or Mn, or combinations thereof.” (Emphasis added). Support for this amendment may be found at least in previously presented claim 25. In contrast, none of these metals are disclosed in Mattes. Instead, Mattes discloses that the radionuclides used for labeling may be I^{125} , I^{131} , ^{32}P , ^{77}Br , ^{225}At , ^{213}Bi , ^{111}In , and ^{188}Rh . Mattes, col. 2, ll. 29-40. Accordingly, for at least this additional reason, Mattes cannot anticipate independent claim 32.

In the Advisory Action, the Examiner stated that “the claims do not appear to require the limitation of the intercalating moiety being ‘multi-dentate ligand’ nor do the claims appear to require the limitation of the intercalating moiety being coordinated through more than one bond to the metal.” Advisory Action, pp. 3-4. Applicants respectfully agree with the Examiner that the claims, as presented prior to the present amendments, did not require a bi- or multi-dentate coupling to the metal. Accordingly, to

clarify this feature, independent claim 40 is amended to recite “a metal complexed with the ligand attached to the intercalating moiety, wherein the ligand and the intercalating moiety provide at least a bidentate coupling to the metal.” (Emphasis added). Support for this amendment may be found at least in FIGS. 1 and 2, which illustrate numerous bidentate complexes wherin metal ions are coupled to both the intercalating moiety and the attached ligand. Specification, FIGS. 1 and 2. Further support may be found in the specification, which recites that “of several mono- and bidentate ligands (especially picolinic acid) 5,6-banzochinolin-3-carboxylic acid was selected as intercalator,” in Example 1. *Id.* at para. [0036]; FIG. 2.

In contrast to bidentate coupling to both the attached ligand and intercalating moiety, as recited in amended independent claim 40, Mattes teaches a “radiolabeled nucleic acid-targeting small molecule.” Mattes, p. 6, ll. 14-16. The radiolabels on the small molecules of Mattes are not disclosed as having a bidentate coupling to the ligand attached to the intercalating moiety and the intercalating moiety, or, indeed, any multiple coupling at all, but are disclosed as being covalently bound to a single carbon on the small molecule. *Id.* at col. 2, ll. 29-32 (which states that “a preferred form of the invention is a nucleic acid-binding or DNA-intercalating small molecule labeled with one or more of I¹²⁵, I¹³¹, and ³²P or both.”). Further, Mattes states that the radiolabeled small molecules can be produced by standard oxidative iodination. *Id.* at col. 2, ll. 41-45. Although Mattes discloses a list of radionuclides, including two metals, which are claimed to work as radiolabels, Mattes discloses no bi- or multi-dentate ligands. *Id.* at col. 2, l. 40.

Thus, Mattes does not teach or disclose that the “ligand and the intercalating moiety provide at least a bidentate coupling to the metal,” as recited in amended independent claim 40. Accordingly, for at least this additional reason, Mattes cannot anticipate independent claim 40.

Finally, new claim 54 depending from independent claim 51 has been added. The claim recites a number of specific structures that may be used in the present techniques. Support for claim 54 may be found in the current application at least in FIGS. 1 and 2. None of these structures, nor any similar structures, are taught or disclosed in Mattes. Accordingly, Mattes cannot anticipate new claim 54.

As noted in the legal precedent section, the reference must disclose the identical invention in as complete detail as in the claims to support a *prima facia* case for anticipation. *Richardson*, 9 U.S.P.Q.2d at 1920. As discussed above, Mattes does not disclose all of the limitations of amended independent claims 22, 32, 40, and 51, or of new dependent claim 54 and cannot anticipate these claims. For the same reasons, among others, Mattes cannot anticipate claims 23-29, 33-37, 41-50, 52, and 53, which depend from claims 22, 32, 40, and 51. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of these claims under 35 U.S.C. §102, and allow the claims to issue.

Claim Rejections under 35 U.S.C. § 103(a)

In the Advisory Action, the Examiner maintained the rejection of claims 30, 31, 38, and 39 under 35 U.S.C. § 103(a) as being unpatentable over Mattes, “as applied to claims 22-29, 32-37 and 40-53 above,” in view of Holley et al. (Cancer Research 1992; 52: 4190-4195, hereinafter “Holley”). Advisory Action, p. 4. Applicants respectfully traverse this rejection.

Legal Precedent

The burden of establishing a *prima facie* case of obviousness falls on the Examiner. *Ex parte Wolters and Kuypers*, 214 U.S.P.Q. 735 (B.P.A.I. 1979). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Mattes and Holley, taken alone or in hypothetical combination, fail to disclose all of the elements of the present claims.

Turning to the claims, claims 30 and 31 ultimately depend from independent claim 22, while claims 38 and 39 ultimately depend from independent claim 32. The Examiner notes that "Mattes does not explicitly teach that tumor seeking molecule is spermidine." Office Action, p. 6. However, the Examiner claims that the chlorambucil-spermidine conjugate of Holley would make the use of spermidine obvious. *Id.*

However, as discussed with respect to the rejection under 35 U.S.C. § 102, Mattes does not teach or suggest "wherein the intercalating moiety is functionalized with a ligand configured to coordinate a $[\text{metal}(\text{CO})_3]^+$ moiety; and a metal complexed with the ligand attached to the intercalating moiety," as recited in both amended independent claims 22 and 32. Further, Mattes also does not teach or suggest that "the metal comprises Tc-99m, Re-186, Re-188, or Mn, or combinations thereof," as recited in independent claim 32. Holley, either individually, or in any sort of hypothetical combination with Mattes, does not obviate this deficiency. Instead, Holley is merely cited by the Examiner for the teaching of a spermidine in a hypothetical combination with the conjugate of Mattes. Advisory Action, p. 4.

Accordingly, independent claims 22 and 32 are allowable over Mattes in view of Holley. As claims 30 and 31 depend from claim 22 and claims 38 and 39 depend from claim 32, these claims are allowable for at least the same reasons as discussed above. Therefore, Applicants respectfully request withdrawal of the rejection of claims 30, 31, 38 and 39 under 35 U.S.C. § 103.

CONCLUSION

Applicants respectfully submit that all pending claims should be in condition for allowance. However, if the Examiner believes certain amendments are necessary to clarify the present claims or if the Examiner wishes to resolve any other issues by way of a telephone conference, the Examiner is kindly invited to contact the undersigned attorney at the telephone number indicated below.

Authorization for Extensions of Time and Payment of Fees

Applicants respectfully request a two-month extension for this reply. In accordance with 37 C.F.R. § 1.136, Applicants hereby provide a general authorization to treat this and any future reply requiring an extension of time as incorporating a request thereof. The Commissioner is authorized to charge the requisite fee of \$460 for the extension of time, \$50 for one additional dependent claim, \$810 for the Request for Continued Examination, and any additional fees which may be required, to Deposit Account no. 13-1160.

Respectfully submitted,

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